

are counteracted by ETRAs targeting ETB but not ETA receptors. ETB receptors may also regulate ET-1 levels through changes in ECE-1 expression. We postulate that higher concentrations of treprostinil may be required to reach clinical efficacy in PAH when combined with non-specific ETRAs.

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### Potential involvement of functional tricuspid regurgitation in the diagnostic error to assess pulmonary arterial pressure by Doppler echocardiography

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**Background:** Transthoracic Doppler echocardiography (DE) is useful for the screening of pulmonary hypertension (PH), which is often treated by endothelin antagonist, although recent studies have suggested that estimation of pulmonary artery pressure (PAP) by DE is frequently inaccurate. This study aimed to examine that functional tricuspid regurgitation (TR) with geometric alterations caused by right ventricular dilatation is involved in the diagnostic error of echocardiography for the assessment of PAP. **Methods:** We conducted a retrospective cohort study of consecutive 127 patients (male,  $n = 58$ , mean age of 55 years) who received both echocardiography and right heart catheterization (RHC) during the 2-year period from November 2008 to October 2010. We defined PH as mean PAP  $> 25$  mmHg at rest by RHC and "accurate estimated echocardiographic value" when it remained within 10 mmHg of the invasive measurement. **Results:** A total of 75 patients (59%) were diagnosed to have PH by RHC. When the patients were divided into 3 groups; accurate ( $n = 52$ ), over-estimate ( $n = 63$ ) and under-estimate ( $n = 12$ ), the diagnosis of PH by RHC was 42% in accurate, 68% in over-estimate, and 83% in under-estimate groups ( $P = 0.004$ ). In echocardiography, right ventricular dimension was significantly larger in over-estimate group (accurate,  $30.0 \pm 5.7$  mm; over,  $35.3 \pm 8.6$  mm; under,  $32.8 \pm 5.2$  mm,  $P = 0.002$ ), and the severity of TR was significantly worse in over-estimate group ( $P < 0.0001$ ). Right atrium tended to be larger in both over-estimate and under-estimate groups than accurate group (accurate,  $38.8 \pm 5.7$  mm; over,  $42.6 \pm 8.49$  mm; under,  $42.7 \pm 6.2$  mm,  $P = 0.073$ ). **Conclusions:** Our results indicate that the accuracy of DE is not enough for PAP evaluation, particularly in patients with PH associated with increased TR grading and enlarged right heart dimension.

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### Detection of developing pulmonary vasculopathy with non-invasive cardiopulmonary exercise testing

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Since the discovery of ET-1, over-expression of ET-1 has been demonstrated in patients with pulmonary arterial hypertension (PAH). In contrast to chronic thromboembolic pulmonary hypertension (CTEPH), patients with PAH have pulmonary vasculopathy (PV). PV leads to impaired dilatation of affected pulmonary vessels,

impeding the increase of cardiac output (CO) and stroke volume (SV) during exercise. Peak  $O_2$  uptake shows CO, and peak  $O_2$ -pulse shows SV during cardiopulmonary exercise testing (CPX). To investigate the increase of CO during exercise, we performed CPX in 12 patients with PAH and 7 patients with CTEPH. Predicted peak  $O_2$  uptake ( $45.5 \pm 8.0$  vs.  $60.6 \pm 13.4\%$ ,  $p < 0.01$ ) and predicted peak  $O_2$ -pulse ( $55.6 \pm 7.6$  vs.  $69.1 \pm 6.9\%$ ,  $p < 0.01$ ) were significant higher in CTEPH than PAH. Diffusion capacity for carbon monoxide (%DLco:  $40.3 \pm 13.7$  vs.  $62.2 \pm 13.9\%$ ,  $p < 0.01$ ) was also significantly higher in CTEPH than PAH, however there was no correlation between %DLco and peak  $O_2$  uptake or peak  $O_2$ -pulse. While, there was no difference in mean pulmonary arterial pressure (mPAP:  $31 \pm 6.8$  vs.  $30.1 \pm 7.0$  mmHg, n.s.), cardiac output (CO:  $4.1 \pm 0.6$  vs.  $4.4 \pm 0.4$  L/min, n.s.), and pulmonary vascular resistance (PVR:  $5.2 \pm 2.0$  vs.  $5.2 \pm 2.8$  wood units, n.s.) at rest. Our data indicate that, regardless of hemodynamic, both lower peak  $O_2$  uptake and peak  $O_2$ -pulse show PV impeding the increase of CO during exercise. CPX can predict the onset of PAH by detection of PV in early stage.

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### Vascular endothelial growth factor (VEGF) and the control of endothelin-1 synthesis by human lung microvascular endothelial cells: A possible pathway for pathogenesis

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**Introduction:** Increased endothelin-1 (ET-1) is a hallmark of pulmonary arterial hypertension (PAH), and contributes to its pathogenesis. The factors controlling ET-1 in PAH are poorly understood. Vascular endothelial growth factor (VEGF) blockade results in PAH-like lesions in animal models, and has caused PAH in humans. The effects of VEGF on ET-1 production by human lung blood microvascular endothelial cells (HMVEC-LBI) are unknown. **Methods:** We exposed HMVEC-LBI (Lonza Inc.) in-vitro to human VEGF121 (40 ng/ml) in serum-free medium for 7 h, in the absence or presence of the VEGF receptor antagonist, SU5416 (Cayman Chemical, 3 and 10  $\mu$ M). ET-1 production was measured in the supernatant. Phosphorylation of VEGF receptor 2 (VEGFR2) was measured by western blotting after exposure to VEGF  $\pm$  SU5416 for 5 and 10 min. **Results:** VEGF effectively caused VEGFR2 phosphorylation, which was blocked by SU5416. VEGF decreased ET-1 production by 29%. In the absence of VEGF, SU5416 increased ET-1 production, by 16% at 10  $\mu$ M, and SU5416 was able to completely abolish the VEGF effect on ET-1 production. **Conclusion:** VEGF may promote vascular health by decreasing ET-1 production in HMVEC-LBI. Blockade of VEGF signalling by SU5416 increases ET-1 levels and may thereby contribute to the pathogenesis of pulmonary hypertension seen with VEGF blockade.

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### Effect of bosentan on exercise capacity in patients with pulmonary arterial hypertension or inoperable chronic thromboembolic pulmonary hypertension

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